

## Clinical Article

# Effects of cerebral perfusion pressure and increased fraction of inspired oxygen on brain tissue oxygen, lactate and glucose in patients with severe head injury

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## Summary

**Objective.** The purpose of the study was to measure the effects of increased inspired oxygen on patients suffering severe head injury and consequent influences on the correlations between CPP and brain tissue oxygen (PtiO<sub>2</sub>) and the effects on brain microdialysate glucose and lactate.

**Methods.** In a prospective, observational study 20 patients suffering severe head injury (GCS ≤ 8) were studied between January 2000 and December 2001. Each patient received an intraparenchymal ICP device and an oxygen sensor and, in 17 patients brain microdialysis was performed at the cortical-subcortical junction. A 6 h 100% oxygen challenge (FiO<sub>2</sub> 1.0) (*Period A*) was performed as early as possible in the first 24 hours after injury and compared with a similar 6 hour period following the challenge (*Period B*). Statistics were performed using the linear correlation analysis, one sample t-test, as well as the Lorentzian peak correlation analysis.

**Results.** FiO<sub>2</sub> was positively correlated with PtiO<sub>2</sub> ( $p < 0.0001$ ) over the whole study period. PtiO<sub>2</sub> was significantly higher ( $p < 0.001$ ) during *Period A* compared to *Period B*. CPP was positively correlated with PtiO<sub>2</sub> ( $p < 0.001$ ) during the whole study. PtiO<sub>2</sub> peaked at a CPP value of 78 mmHg performing a Lorentzian peak correlation analysis of all patients over the whole study. During *Period A* the brain microdialysate lactate was significantly lower ( $p = 0.015$ ) compared with *Period B*. However the brain microdialysate glucose remained unchanged.

**Conclusion.** PtiO<sub>2</sub> is significantly positively correlated with FiO<sub>2</sub>, meaning that PtiO<sub>2</sub> can be improved by the simple manipulation of increasing FiO<sub>2</sub> and ABGAO<sub>2</sub>. PtiO<sub>2</sub> is positively correlated with CPP, peaking at a CPP value of 78 mmHg. Brain microdialysate lactate can be lowered by increasing PtiO<sub>2</sub> values, as observed during the oxygen challenge, whereas microdialysate glucose is unchanged during this procedure. Extension of the oxygen challenge time and measurement of the intermediate energy metabolite pyruvate may clarify the metabolic effects of the intervention. Prospective comparative studies, including analysis of outcome on a larger multicenter basis, are necessary to assess the long term clinical benefits of this procedure.

**Keywords:** Traumatic brain injury; brain tissue oxygen; energy metabolites; hyperoxygenation.

## Introduction

Evidence that cerebral blood flow (CBF) is decreased but oxygen consumption is increased in the acute phase after severe brain injury [4, 26, 27, 41] suggests that treatment aimed at preventing cerebral ischaemia may improve outcome. Secondary mechanisms, such as neuroexcitotoxicity can worsen brain swelling and intracranial pressure (ICP), further impairing cerebral perfusion pressure (CPP) and brain oxygenation [9, 19, 23, 24, 47]. The challenge, therefore, is two-fold, to maintain sufficient blood supply to the brain and to improve oxygen delivery to brain cells [38, 63, 67]. A consensus has been reached that CPP of around 70 mmHg may provide optimal blood supply to the brain [43]. In contrast, there is no definition of the optimal values for the fraction of inspired oxygen (FiO<sub>2</sub>) or for brain tissue oxygen tensions (PtiO<sub>2</sub>).

Measurements of PtiO<sub>2</sub>, using various commercially available sensors, can provide a continuous assessment of brain oxygenation and microdialysis enables monitoring of brain energy metabolites including lactate concentration. The role of intracerebral lactate after head injury has been much debated recently [5]. It has been hypothesized that lactate constitutes the preferred substrate over glucose in neurons, especially in times of increased metabolism [30–32, 55–57]. This is because neurons use lactate by converting it to pyruvate which then enters the mitochondrial Krebs-cycle to produce ATP [5], as long as mitochondria are functioning

[14, 58]. Thus, an increased lactate level may have a dual significance: it may be either a sign of anaerobic metabolism, or of hyperglycolysis independent of aerobic conditions.

Although an  $\text{FiO}_2$  of 0.4 is usually employed in intubated and mechanically ventilated patients to maintain 100% oxygen blood saturation, higher values have been proposed. A number of groups have analyzed the relation between arterial oxygen tension (ABGAO<sub>2</sub>) and PtiO<sub>2</sub> in patients with severe head injury [3, 37, 52] and Menzel *et al.* reported that, by increasing ABGAO<sub>2</sub> through ventilatory oxygen enhancement, PtiO<sub>2</sub> was elevated also [35].

WE hypothesized that, by increasing  $\text{FiO}_2$  from 0.4 to 1.0, PtiO<sub>2</sub> would be improved and that this might influence brain metabolism as reflected in measurements of glucose and lactate production. We report studies aimed to test this hypothesis through observation of the effects of increasing  $\text{FiO}_2$  to 1.0 for 6 hours in a group of severely head injury patients. The studies were made in the first day after injury, as soon as possible after stabilization of the monitoring sensors and we also analyzed the relationship between CPP and PtiO<sub>2</sub>.

## Materials and methods

A total of 20 patients who had suffered a severe head injury, with a Glasgow coma score  $\leq 8$ , were included in the study. The study protocol was approved by the local Ethics Committee for Human Research. Informed consent was obtained from the families of the patients. All patients were directly referred to our centre either by helicopter or by ambulance in the first 3 hours after trauma, were intubated, sedated and treated to relax muscles. At the time of admission patients were ventilated with  $\text{FiO}_2$  1.0. A cranial CT scan was performed as soon as possible. A patient who was not expected to survive the next 24 hours was excluded from this study, but was treated according to our standard protocol. If an emergency operation was not required, cranial bolts for measurement of PtiO<sub>2</sub>, ICP and a brain microdialysis catheter were introduced. If a patient required an emergency operation, the sensors were placed in the operating theatre after closure of the skin. A run-in-time with the Licox sensor and the microdialysis sensor of between one to two hours after insertion was allowed before collection of data for analysis. For data monitoring, a mobile intensive care HP<sup>®</sup> monitor was upgraded with an interface for the multi-modality-monitor MMM (Licox<sup>®</sup> GMS, Germany). After the study period, the data were downloaded onto a computer. Microsoft<sup>®</sup> Access and Excel programs were used for data storage and processing. The indices collected were mean arterial blood pressure (MABP), end-tidal CO<sub>2</sub> (EtCO<sub>2</sub>), CPP, ICP, PtiO<sub>2</sub>, core temperature and heart rate.

### *Oxygen challenge period in the first 24 hours after injury (period A)*

The 6 hour “oxygen challenge test” was started as soon as the “run-in-time” for the sensors was over. The patient was ventilated with an  $\text{FiO}_2$  of 1.0; thereafter,  $\text{FiO}_2$  was gradually reduced to the usual values (0.4) according to standard management.

### *Period following oxygen challenge (period B)*

For comparison we used the 6 hour period immediately following the oxygen challenge period A and named it period B. Data collection was not different to Period A.

### *Baseline $\text{FiO}_2$*

$\text{FiO}_2$  values before to Period A were around 0.6. After the oxygen challenge Period A,  $\text{FiO}_2$  was reduced to 0.6 and from there stepwise to baseline values ( $\text{FiO}_2$  0.3–0.4) that depended on the patient's condition.

### *Bolts and ICP sensor*

A commercially available intraparenchymal ICP transducer (Integra<sup>®</sup> Neurosciences, Camino, San Diego, California, USA) was used and fixed to the frontal skull.

### *Licox*

For measurement of the oxygen tension in brain tissue, the Licox oxygen sensor with a 13 mm<sup>2</sup> sensitive area (Licox, Integra<sup>®</sup> Neurosciences) was used in each of the 20 patients. The sensor was introduced, along with a microdialysis catheter, into a separate burr hole. The data were collected online through the Licox Multimodal Monitor MMM. The sensor was placed in the frontal area, in an area of brain judged by the first CT not to be contused.

### *Microdialysis*

A custom microdialysis probe (CMA<sup>®</sup>, Sweden), with a molecular mass cut-off level of 20 kDa, was used along with the Licox probe. The microdialysis probe was perfused using a CMA microdialysis pump with saline at a flow rate of 0.5  $\mu\text{l}/\text{min}$ . Samples were collected every hour. The samples were then frozen for later analysis for glucose and lactate using an automated enzymatic assay with the YSI 2700 (Yellow Springs<sup>®</sup>, USA). At the end of the study, the microdialysis probes were collected and inspected for leakage and kept for measurement of the in vitro recovery rates for glucose and lactate. A sample volume of 25  $\mu\text{l}$  in total was needed for the analysis for glucose and lactate with the YSI 2700.

### *Data collection and storage*

The data were collected online using a Hewlett Packard<sup>®</sup> ICU Monitor mounted on a mobile unit and upgraded with an interface to enable connection to the Licox<sup>®</sup> MMM. The data were downloaded on to an Acer<sup>®</sup> Notebook at a frequency of 2 per minute. For the 20 patients, 160812 separate data points were collected; these represented a total of 80406 minutes of monitoring. Data were stored in a Microsoft<sup>®</sup> Access database.

### *Statistical analysis*

To assess correlations between  $\text{FiO}_2$ , ABGAO<sub>2</sub> and CPP versus PtiO<sub>2</sub>, we calculated the r-values for each patient the 24 h observation period. Thereafter, a one sample t-test was run over the r-values to calculate the significance. To analyze the 2 observation periods A and B for  $\text{FiO}_2$  and ABGAO<sub>2</sub> versus PtiO<sub>2</sub>, the means of the 6 hour oxygen challenge period (A) and of the 6 hours after the oxygen challenge period (B) were calculated for each patient. A paired t-test over the mean values of all patients was run to assess the significances of any differences. For calculation of the peak correlation analysis between CPP and PtiO<sub>2</sub> in all patients, Lorentzian peak regression analysis was used [33]. To determine

the significance of any differences in lactate during the two observations periods (A and B), an ANOVA test was used. For all results the threshold of significance was set at a p-value of 0.05. The calculations were done using Sigma Plot 2001<sup>®</sup>, SPSS<sup>®</sup> and Statistica<sup>®</sup>.

Results

A total of 20 patients suffering from severe head injury were studied, 13 males ( $40 \pm 16$  years) and 7 females ( $37 \pm 20$  years). The average initial Glasgow Coma Score was 6. The demographic data are summarized in Table 1. The intracerebral sensors (Licox and ICP) were placed in 17 cases on the right frontal side and in 3 cases on the left

frontal side. Microdialysis was placed in 19 patients; the samples were used for analysis in 15 patients. In 2 cases the dialysate showed a red discoloration indicating the sensor was ruptured, the samples were discarded. Five patients required immediate surgery.

Fraction of inspired oxygen and arterial blood gas oxygen versus PtiO<sub>2</sub>

FiO<sub>2</sub> and PtiO<sub>2</sub> were significantly positively correlated ( $p < 0.0001$ ) (t-test over the r-values from the correlation of all patients in the first 24 hours (Fig. 1a). A similar

Table 1. Demographic data. Probe placement refers to the location of the ICP, PtiO<sub>2</sub> and microdialysis sensors

| Patient | Age | Sex    | Initial GCS | Probe placement | Injury type        | Emergency op. |
|---------|-----|--------|-------------|-----------------|--------------------|---------------|
| 1       | 25  | male   | 4           | right frontal   | DIA                | 0             |
| 2       | 56  | male   | 6           | right frontal   | SDH and DIA        | 1             |
| 3       | 24  | female | 3           | right frontal   | DIA                | 0             |
| 4       | 59  | male   | 6           | right frontal   | DIA                | 0             |
| 5       | 21  | female | 9           | right frontal   | DIA                | 0             |
| 6       | 28  | male   | 6           | right frontal   | DIA                | 0             |
| 7       | 69  | male   | 4           | right frontal   | DIA bifronto-basal | 0             |
| 8       | 17  | male   | 6           | right frontal   | DIA                | 0             |
| 9       | 53  | male   | 9           | right frontal   | EDH and DIA        | 1             |
| 10      | 22  | female | 9           | right frontal   | DIA                | 0             |
| 11      | 73  | female | 8           | right frontal   | DIA                | 0             |
| 12      | 51  | male   | 9           | right frontal   | SDH and DIA        | 2             |
| 13      | 21  | male   | 3           | right frontal   | DIA                | 0             |
| 14      | 48  | female | 10          | left frontal    | DIA                | 0             |
| 15      | 25  | male   | 4           | right frontal   | DIA                | 0             |
| 16      | 22  | female | 7           | right frontal   | DIA                | 0             |
| 17      | 41  | male   | 6           | left frontal    | SDH and DIA        | 1             |
| 18      | 54  | female | 3           | right frontal   | SDH and DIA        | 1             |
| 19      | 28  | male   | 3           | left frontal    | DIA                | 0             |
| 20      | 48  | male   | 8           | right frontal   | DIA                | 0             |

DIA Diffuse axonal Injury, SDH Subdural hematoma, EDH Epidural hematoma.

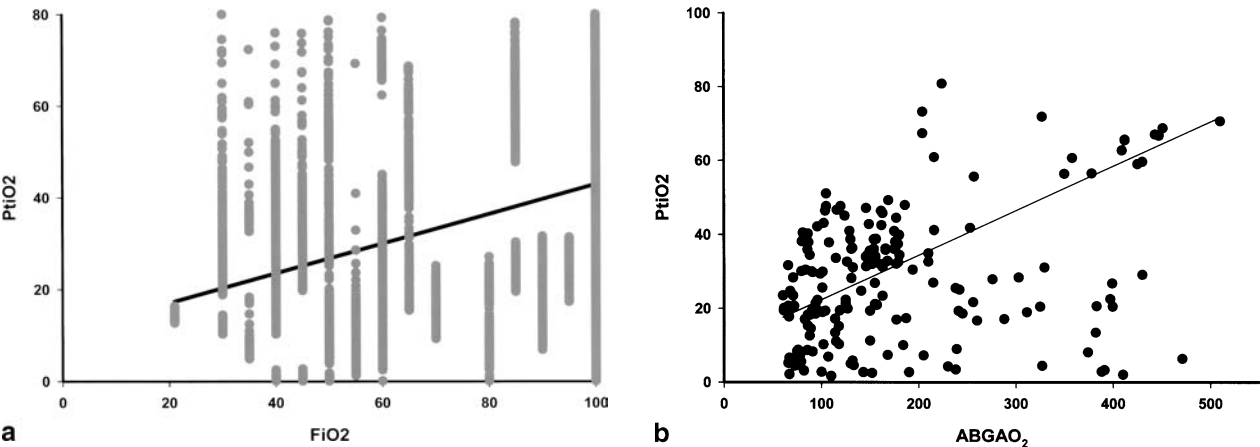


Fig. 1. (a) Combined regression analysis between FiO<sub>2</sub> and PtiO<sub>2</sub> of all patients after TBI. Test t-test over the r-values of each patient showed a significance of  $p < 0.0001$ . (b) Combined regression analysis between ABGAO<sub>2</sub> and PtiO<sub>2</sub> of all patients after TBI ( $r = 0.5$ ). The t-test on the r-values of each patients showed a significance of  $p < 0.0001$

significant positive correlation between ABGAO<sub>2</sub> and PtiO<sub>2</sub> was observed ( $p < 0.0001$ ). The  $r$ -value of the combined data of all patients in one plot is  $r = 0.5$ , as shown in Fig. 1b.

Of a sub-group of 6 patients with low PtiO<sub>2</sub> ( $< 10$  mmHg) and high ABGAO<sub>2</sub> and FiO<sub>2</sub> (1.0) during monitoring (Figs. 1a and 1b), 4 died in ICU. The other 2 patients had low PtiO<sub>2</sub> levels from the start and reacted more slowly to an increase in FiO<sub>2</sub>. The Licox probes were in the vicinity of haemorrhagic contusions in these cases.

The stability of PtiO<sub>2</sub> over the Period A is shown as the percentage change over the 6 hours in relation to the values of the first 10 minutes of Period A (Fig. 2).

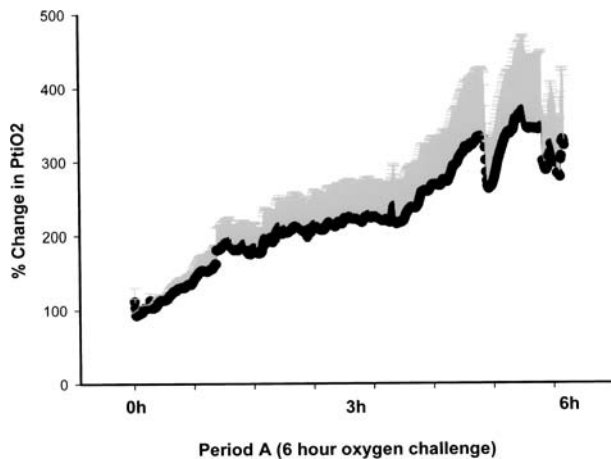


Fig. 2. Mean percentage increase in PtiO<sub>2</sub> (+SEM) during the Period A (FiO<sub>2</sub> 1.0) of all 20 patients. The reference is the first 10 minutes of Period A

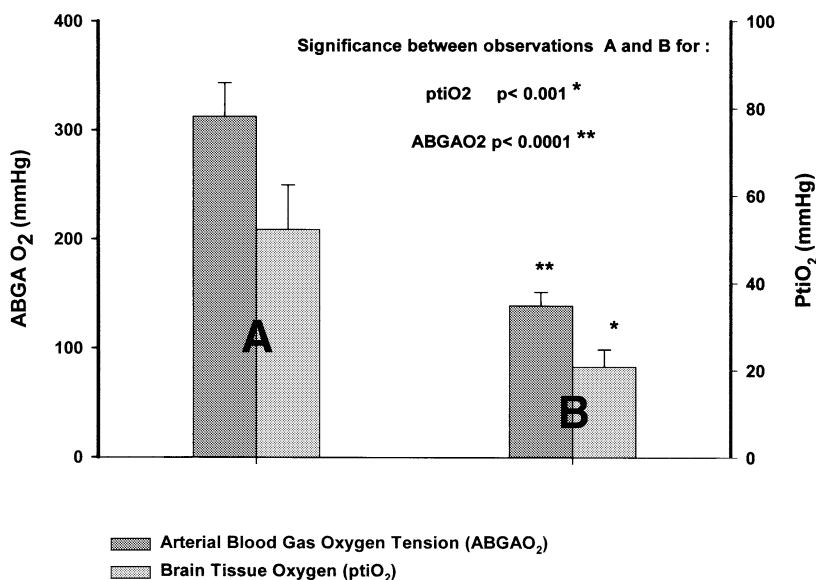


Fig. 3. Oxygen challenge (period A) and comparison of ABGAO<sub>2</sub> and PtiO<sub>2</sub> in the subsequent period B, ABGAO<sub>2</sub> and PtiO<sub>2</sub> were significantly higher in A than in B

### 6 hour oxygen challenge and PtiO<sub>2</sub>–ABGAO<sub>2</sub>

PtiO<sub>2</sub> was significantly higher ( $p < 0.001$ ) during period A ( $52.3 \pm 10.1$ ) as compared to period B ( $20.7 \pm 3.9$ ). ABGAO<sub>2</sub> was similarly higher during period A ( $p < 0.0001$ ) (Fig. 3).

### Analysis of cerebral perfusion pressure versus PtiO<sub>2</sub>

The analysis of cerebral perfusion pressure versus PtiO<sub>2</sub> showed a significant positive correlation ( $p < 0.001$ ) (t-test of the  $r$ -values of all patients). Analyzing all patients together in one plot with a Lorentzian peak correlation analysis, demonstrated a peak of PtiO<sub>2</sub> at a CPP of 78 mmHg (Fig. 4).

### The 6 hour oxygen challenge brain microdialysate glucose and lactate dynamics

The dialysate lactate values during period A were significantly lower ( $p = 0.015$ ) than during period B (ANOVA Test) (Fig. 5). Analysis of dialysate glucose levels did not show significant difference (Fig. 6).

The mean values and standard deviations of the values of MABP, ICP, CPP and EtCO<sub>2</sub> during periods A and B are listed in Table 2.

### Relationship between EtCO<sub>2</sub> and arterial blood gas oxygen values

The online measured EtCO<sub>2</sub> values were 8.1 mmHg lower than the directly measured arterial blood gas oxygen tensions ( $n = 1365$ ), confirming that the patients

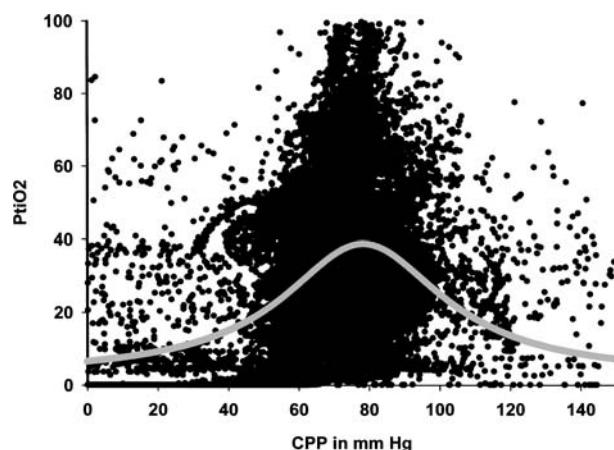


Fig. 4. Lorentzian peak correlation analysis between CPP and PtiO<sub>2</sub> of all patients in one plot, showing a peak in best PtiO<sub>2</sub> at a CPP value of 78 mmHg

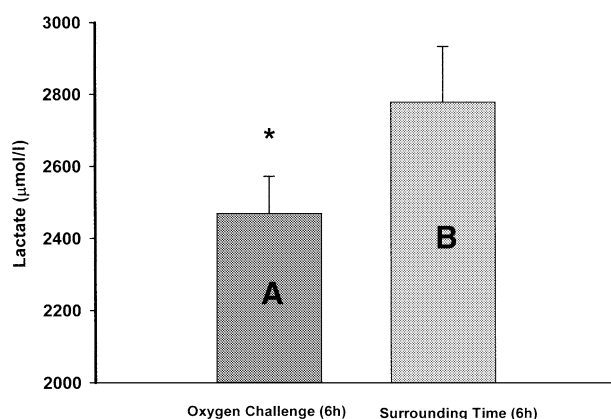


Fig. 5. Bar plot comparing dialysate lactate during the oxygen challenge period and the subsequent time when dialysate lactate was higher ( $p = 0.015$ )

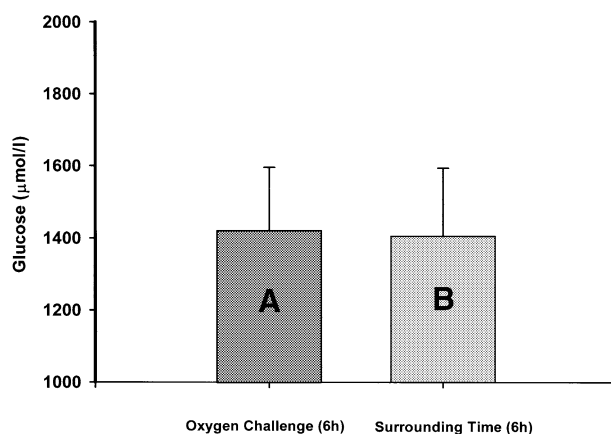


Fig. 6. Bar plot comparing dialysate glucose during the oxygen challenge period and the subsequent time

Table 2. Hemodynamic data (mean values and the standard deviations) during Period A and Period B

|                   | A    |      | B    |      |
|-------------------|------|------|------|------|
|                   | Mean | SD   | Mean | SD   |
| MAP               | 86.4 | 14.8 | 81.4 | 14.0 |
| ICP               | 17.2 | 15.4 | 18.3 | 17.5 |
| CPP               | 69.3 | 14.9 | 63.1 | 18.5 |
| PECO <sub>2</sub> | 26.9 | 4.1  | 28.2 | 3.9  |

$n = 17104$ .

MABP Mean arterial blood pressure; ICP intracranial pressure; CPP cerebral perfusion pressure; EtCO<sub>2</sub> end tidal CO<sub>2</sub>.

were moderately hyperventilated according to our guidelines (Table 2).

## Discussion

Our study demonstrates that an increase in FiO<sub>2</sub> can lead to a significant increase in arterial blood gas oxygen tensions (ABGAO<sub>2</sub>) and brain tissue oxygen tensions (PtiO<sub>2</sub>) in recently head injured patients. Furthermore, increasing FiO<sub>2</sub>, and hence increasing PtiO<sub>2</sub>, was associated with a decreased brain microdialysis lactate, without a change in brain microdialysis glucose. CPP was positively correlated with PtiO<sub>2</sub> with a peak at a CPP-value of 78 mmHg.

## General considerations

This study was performed prospectively, excluding patients unlikely to survive the first 24 hours. This is one reason that fewer patients with very low PtiO<sub>2</sub> values were included, as compared to those reported in other studies of similar severely head injured patients [3, 69]. In our study, each patient was their own control for the microdialysis results. We chose this design of study because baseline values for microdialysis, glucose and lactate differ in different patients with a severe head injury, as a result of different types of injury. To reduce these effects, microdialysis sensors and oxygen sensors were placed in non-contused areas. However, contusions sometimes develop after a delay and the use of multiple probe placement has been proposed to gain a more global view of changes in brain metabolism [25, 60].

The sequence of observations, i.e. Period A to Period B, is likely to have influenced our findings. FiO<sub>2</sub> was decreased only after the oxygen challenge so that the difference in brain tissue microdialysis lactate values might have been greater between Period A and Period B. We plan to expand the present protocol and study a

“real” control group, in which there is no oxygen enhancement.

Two different probes are in clinical use to measure brain tissue oxygen tensions: the Clark type electrode as used in the Licox<sup>®</sup> and, previously, Paratrend<sup>®</sup> probes, and an optical system as used in the Neurotrend<sup>®</sup>. Different dynamics of oxygen measurement and different effects of increasing FiO<sub>2</sub> have been described for the two systems, and studies testing the sensors simultaneously are ongoing [46, 22].

#### *Fraction of inspired oxygen and brain tissue oxygen*

There are reports of a positive correlation between values of PtiO<sub>2</sub> and of different induced arterial oxygen tensions [29, 37, 66, 70]. Thus, Van Santbrink *et al.* and Menzel *et al.* described an increasing brain tissue oxygen in patients with severe head injury in response to increasing arterial oxygen tensions [36, 66]. Differences in baseline values of PtiO<sub>2</sub> and in how these respond to increased arterial oxygen tensions may result from the use of different oxygen sensors placed at different depths and in different areas of the brain. In our study the sensor was placed at the same depth, in relation to the bolt system, in each patient.

Low brain tissue oxygen tensions have been associated with poor outcome (PtiO<sub>2</sub> < 20 mmHg) and fatal outcomes (PtiO<sub>2</sub> < 10 mmHg) [3, 16]. Van den Brink *et al.* [65] reported low PtiO<sub>2</sub> in 57% of patients with severe head injury despite full treatment. Our demonstration that, if PtiO<sub>2</sub> values remain low, despite an oxygen challenge (FiO<sub>2</sub> 1.0), most patients died, may help to identify very severe injury. On the other hand, it has also been demonstrated that a marked increase in brain tissue oxygen after inducing FiO<sub>2</sub> 1.0 can be associated with a poor outcome [35, 66]. This has been linked to impaired cerebral vasoreactivity. Normally arterial hyperoxia causes vasoconstriction and there is about a 20% reduction of CBF when ventilation with FiO<sub>2</sub> 1.0 is used, as long as vasoreactivity is maintained [48]. This suggests that an oxygen reactivity challenge might help to identify patients who might benefit from early increased oxygen ventilation, but more data are needed.

#### *Microdialysis glucose and lactate*

There is evidence from studies using microdialysis that neuroexcitatory induced hyperglycolysis occurs

after experimental head injury [11–13]. Glutamate released by neurons after injury is taken up by astrocytes and Pellerin and Magestretti hypothesized that this drives glycolysis. This may relate to the hyper glycolysis observed with PET in patients suffering severe head injury [4, 45] and in accord with findings with microdialysis of increased glutamate and lactate and reduced glucose [9, 18]. This neuroexcitotoxic response occurs very soon after injury and may be missed in the clinical circumstances. Menzel *et al.* performed studies in a similar time period after severe head injury but placed less emphasis on an immediate start and included a hyperoxygenation challenge [36]. Lactate levels in the microdialysis fluid were reduced during the oxygen challenge period, and glucose showed a trend to lower values. Overall the values they observed with microdialysis were lower than the values reported in our study. This difference may be caused by the different microdialysis flow rates used, 2.0 µl/min versus 0.5 µl/min in ours. Rossi and Stocchetti previously commented that the reduction in lactate reported by Menzel *et al.* may be due either to an improvement in aerobic glucose metabolism or simply to a lower oxygen availability as a result of reduction in cerebral blood flow following an increase in arterial blood gas oxygen [50]. However we found no change in glucose levels during the oxygen challenge which suggests an improvement in cerebral glucose utilization. Analysis of pyruvate levels in relation to those of the excitatory transmitter glutamate might elucidate this topic.

#### *Cerebral perfusion pressure and brain tissue oxygen*

As discussed above, the mismatch between cerebral perfusion [7] and metabolic need [4] after TBI can lead to ischaemia, resulting in brain swelling and poor outcome. Prolonged hyperventilation (PaCO<sub>2</sub> < 25 mmHg) has been shown to be associated with a worse outcome and should be used only with additional monitoring of blood flow or oxygenation [21, 53, 54, 65] for which CPP is the best available method. The EBIC Guidelines propose that CPP is maintained between 60–70 mmHg, whereas the ABIC Guidelines support slightly higher values, above 70 mmHg [28, 43]. As definitive evidence is lacking, firm recommendations cannot be made. In our study, CPP was positively correlated with PtiO<sub>2</sub> and the Lorentzian peak correlation analysis demonstrated a peak of PtiO<sub>2</sub> at a CPP value around 78 mmHg. This observation supports the view that CPP

should be maintained over 70 mmHg. However, CPP should not be elevated excessively because the blood brain barrier may be disrupted, which could result in brain edema. Based upon studies of cerebral autoregulation, Czosnyka *et al.* reported a similar value of optimal CPP of around 80 mmHg [15, 61] with higher values possibly disrupting cerebral autoregulation. However interpretation of the results of this Lorentzian peak correlation analysis does not permit conclusions about a definite threshold level for clinical circumstances.

Several studies have analyzed the relation between CPP and PtiO<sub>2</sub>. In an experimental study using a swine model, brain PtiO<sub>2</sub> reflected changes in CPP or CBF [49]. In one clinical study of patients with *mild* to severe head injury, low PtiO<sub>2</sub> could not be predicted on the basis of CPP alone [51], but in another, Bardt *et al.* reported low PtiO<sub>2</sub> values in relation with low CPP values in patients with severe head injury [3]. Stocchetti *et al.* and Bruzzone *et al.* described a relation between CPP and PtiO<sub>2</sub> in areas with disrupted autoregulation in patients with severe head injury and subarachnoid haemorrhage [8, 62]. Taken together, these results suggest that PtiO<sub>2</sub> may be influenced by CPP, independently of tissue demand. This effect may be especially important when autoregulation is disrupted but may have an upper limit after which autoregulation breakthrough may dominate. Measuring the pressure reactivity index online as an index of the state of autoregulation [6], may be helpful in differentiating between patients who can benefit from a more forced CPP therapy, from those for whom therapy aimed at an improvement of blood brain barrier integrity is more appropriate.

### Free radicals

Enhanced free radical production is a major concern of prolonged oxygen therapy and has been demonstrated in ischaemia reperfusion [10, 40, 44] or fluid percussion models [20, 44]. However, the concern is probably not justified, because many studies show no elevation of free radical production following oxygen enhancement [1, 17, 39, 42, 44]. Clinical trials with free radical scavengers such as PEG-SOD and tirilazad-mesylate have neither proved nor disapproved a role for free radicals in head injury [34, 68]. Potentially irreversible lung injury has been described by using an FiO<sub>2</sub> of 1.0 24 to 36 hours [2] and these regimens therefore should be avoided [59, 63, 64].

## Conclusion

Increasing the fraction of inspired oxygen (FiO<sub>2</sub>) is a simple manoeuvre and seems to influence brain metabolism, as shown by the reduction in brain microdialysis lactate. Either alone or in combination with therapies aimed at optimising CPP and/or reestablishment of the blood brain barrier, it may minimize secondary injury following severe head injury. Experimental studies, using standardized trauma models are needed along with multicenter, prospective, randomized, clinical studies with analysis of outcome.

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## References

1. Agardh C, Zhang H, Smith ML, Siesjö BK (1991) Free radical production and ischemic brain damage: influence of postischemic oxygen tension. *Int J Dev Neurosci* 9: 127–138
2. Barber RE, Lee J, Hamilton WK (1970) Oxygen toxicity in man. A prospective study in patients with irreversible brain damage. *N Engl J Med* 283: 1478–1484
3. Bardt T, Unterberg A, Haertl R, Kiening K, Schneider G, Lanksch W (1998) Monitoring of brain tissue PO<sub>2</sub> in traumatic brain injury: effect of cerebral hypoxia on outcome. *Acta Neurochir (Wien) [Suppl]* 71: 153–156
4. Bergsneider M, Hovda D, Shalmon E, Kelly D, Vespa P, Martin N, Phelps M, McArthur D, Caron M, Kraus J, Becker D (1997) Cerebral hyperglycolysis following severe traumatic brain injury in humans: a positron emission tomography study. *J Neurosurg* 86: 241–251
5. Bittar P, Charnay Y, Pellerin L, Bouras C, Magistretti P (1996) Selective distribution of lactate dehydrogenase isoenzymes in neurons and astrocytes of human brain. *J Cereb Blood Flow Metab* 16: 1079–1089
6. Bouma GJ, Muizelaar J, Bandoh K (1992) Blood pressure and intracranial pressure-volume dynamics in severe head injury relationship with cerebral blood flow. *J Neurosurg* 77: 15–19
7. Bouma G, Muizelaar J, Choi S, Newlon P, Young H (1991) Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischemia. *J Neurosurg* 75: 685–693
8. Bruzzone P, Dionigi R, Bellinzona G, Imberti R, Stocchetti N (1998) Effects of cerebral perfusion pressure on brain tissue PO<sub>2</sub> in patients with severe head injury. *Acat Neurochir (Wien) [Suppl]* 71: 111–113
9. Bullock R, Zauner A, Woodward J, Myseros J, Choi S, Ward J, Marmarou A, Young H (1998) Factors affecting excitatory amino

- acid release following severe human head injury. *J Neurosurg* 89: 507–518
10. Cao W, Carney JM, Duchon A, Floyd RA, Chevion M (2002) Oxygen free radical involvement in ischemia and reperfusion injury to brain. *Neurosci Lett* 26: 233–238
  11. Chen T, Qian YZ, Di X, Zhu JP, Bullock R (2000) Evidence of lactate uptake after rat fluid percussion brain injury. *Acta Neurochir (Wien)* [Suppl] 76: 359–364
  12. Chen T, Qian YZ, Rice A, Zhu JP, Di X, Bullock R (2000) Brain lactate uptake increases at the site of impact after traumatic brain injury. *Brain Res* 861: 281–287
  13. Chen T, Qian Y, Di X, Rice A, Zhu J, Bullock R (1999) Lactate/glucose dynamics after rat fluid percussion brain injury. *J Neurotrauma* 17: 135–142
  14. Clausen T, Zauner A, Levasseur J, Rice AC, Bullock MR (2002) Induced mitochondrial failure in the feline brain: implications for understanding acute post-traumatic metabolic events. *Brain Res* 908: 35–48
  15. Czosnyka M, Smielewski P, Piechnik S, Steiner LA, Pickard JD (2001) Cerebral autoregulation following head injury. *J Neurosurg* 95: 756–763
  16. Dings J, Jaeger A, Meixensberger J, Roosen K (1998) Brain Tissue pO<sub>2</sub> and outcome after severe head injury. *Neurol Res* 20: S71–S75
  17. Doppenberg E, Rice MR, Di X, Young H, Woodward J, Bullock R (1998) Increased free radical production due to subdural hematoma in the rat: effect of increased inspired oxygen fraction. *J Neurotrauma* 15: 337–347
  18. Doppenberg E, Zauner A, Bullock R, Ward J (1998) Correlations between brain tissue oxygen tension, carbon dioxide, pH and cerebral blood flow – a better way of monitoring the severely injured brain? *Surg Neurol* 49: 650–654
  19. Fiskum G (2000) Mitochondrial participation in ischemic and traumatic neural cell death. *J Neurotrauma* 17: 843–855
  20. Globus MY, Alonso O, Dietrich D, Busto R, Ginsberg MD (1995) Glutamate release and free radical production following brain injury: effects of posttraumatic hypothermia. *J Neurochem* 65: 1704–1711
  21. Gopinath SP, Valadka A, Uzura M, Robertson C (1999) Comparison of jugular venous oxygen saturation and brain tissue PO<sub>2</sub> as monitors of cerebral ischemia after head injury. *Crit Care Med* 27: 2337–2345
  22. Hoelper B (2002) Unpublished data
  23. Katayama Y, Becker D, Tamura T, Hovda D (1990) Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. *J Neurosurg* 73: 889–900
  24. Katayama Y, Maeda T, Koshinaga M, Kawamata T, Tsubokawa T (1995) Role of excitatory amino acid-mediated ionic fluxes in traumatic brain injury. *Brain Pathol* 5: 427–435
  25. Kiening KL, Schneider GH, Bardt TF, Unterberg AW, Lanksch WR (1998) Bifrontal measurements of brain tissue-PO<sub>2</sub> in comatose patients. *Acat Neurochir (Wien)* [Suppl] 71: 172–173
  26. Levasseur J, Alessandri B, Reinert M, Bullock M, Povlishock J, Kontos H (2000) Fluid percussion injury transiently increases then decreases brain oxygen consumption in the rat. *J Neurotrauma* 17: 101–112
  27. Levasseur J, Qian Y, Alessandri B, Bullock R, Povlishock J, Kontos H (1998) Changes in oxygen utilization after rat fluid percussion injury. *J Neurotrauma* 15: 879
  28. Maas A, Dearden M, Teasdale G, Braakman R, Cohadon F, Iannotti F, Karimi A, Lapierre F, Murray G, Ohman J, Persson L, Servadei F, Stocchetti N, Unterberg A (1997) EBIC-Guidelines for management of severe head injury in adults. *Acta Neurochir (Wien)* 139: 286–294
  29. Maas A, Fleckenstein W, Jong DD (1993) Effect of increased ICP and decreased cerebral perfusion pressure on brain tissue and cerebrospinal fluid oxygen tension. In: Avezaat C, Eijndhoven V, Maas A (eds) *Intracranial pressure VIII*. Springer Berlin Heidelberg New York Tokyo
  30. Magistretti P, Pellerin L (1999) Cellular mechanisms of brain energy metabolism and their relevance to functional brain imaging. *Philos Trans R Soc Lond B Biol Sci* 354: 1155–1163
  31. Magistretti P, Pellerin L, Rothman D, Shulman R (1999) Energy on demand. *Science* 283: 495–497
  32. Magistretti P, Sorg O, Yu N, Martin J, Pellerin L (1993) Neurotransmitters regulate energy metabolism in astrocytes: implications for the metabolic trafficking between neural cells. *Dev Neurosci* 15: 306–312
  33. Marquardt DW (1963) *J Soc Ind Appl Math* 11: 431–441
  34. Marshall LF, Marshall SB (1995) Pitfalls and advances from the international tirizalad trial in moderate and severe head injury. *J Neurotrauma* 12: 929–932
  35. Menzel M, Doppenberg E, Zauner A, Soukup J, Reinert M, Clausen T, Brockenbrough P, Bullock R (1999) Cerebral oxygenation in patients after severe head injury—monitoring and effects of arterial hyperoxia on cerebral blood flow, metabolism and intracranial pressure. *J Neurosurg Anesth* 11: 240–251
  36. Menzel M, Doppenberg E, Zauner A, Soukup J, Reinert M, Bullock R (1999) Increased inspired oxygen concentration improves brain tissue oxygenation and tissue lactate after severe human head injury. *J Neurosurg* 91: 1–10
  37. Menzel M, Rieger A, Roth S, Soukup J, Peuse C, Hennig C, Molnar P, Furka I, Radke J (1998) Simultaneous continuous measurement of pO<sub>2</sub>, pCO<sub>2</sub>, pH and temperature in brain tissue and sagittal sinus in a porcine model. *Acta Neurochir (Wien)* [Suppl] 71: 183–185
  38. Miller JD (1985) Head injury and brain ischaemia – Implications for therapy. *Br J Anaesth* 57: 120–130
  39. Mink R, Dutka AJ (1995) Hyperbaric oxygen after global cerebral ischemia in rabbits does not promote brain lipid peroxidation. *Crit Care Med* 23: 1398–1404
  40. Morimoto T, Globus MY, Busto R, Martinez E, Ginsberg MD (1996) Simultaneous measurement of salicylate hydroxylation and glutamate release in the penumbral cortex following transient middle cerebral artery occlusion in rats. *J Cereb Blood Flow* 16: 92–99
  41. Muizelaar JP (1996) CBF and management of the head-injured patient. In: Narayan R, Wilberger J, Povlishock JT (eds) *Neurotrauma*. McGraw-Hill, New York St. Louis, San Francisco pp 553–561
  42. Murakami N, Horinouchi T, Sakurai M, Ejima Y, Matsukawa S, Kato M, Tabayashi K (2001) Hyperbaric oxygen therapy given 30 minutes after spinal cord ischemia attenuates selective motor neuron death in rabbits. *Crit Care Med* 29: 814–818
  43. The Brain Trauma Foundation (2000) The American Association of Neurological Surgeons. The joint section of neurotrauma and critical care. *J Neurotrauma* 17: 449–627
  44. The Brain Trauma Foundation (2000) The American Association of Neurological Surgeons. The joint section of neurotrauma and critical care. Guidelines for cerebral perfusion pressure. *J Neurotrauma* 17: 507–511
  45. Pellerin L, Magistretti P (1994) Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. *Neurobiology* 91: 10625–10629
  46. Quinones-Hinojosa A, Morabito D, Rollins M, Holland M, Manley GT (2001) In vitro comparison of two different brain tissue oxygen monitors. *J Neurotrauma* 18: 1137
  47. Reinert M, Khaldi A, Doppenberg E, Zauner A, Bullock R (2000) High extracellular potassium and its correlates after severe head



- injury: relationship to high intracranial pressure. *J Neurosurgery* 93: 800–807
48. Rockswold G (1996) Hyperbaric oxygen therapy in head injury. In: Narayan R, Wilberger JR, Povlishock JT (eds) *Neurotrauma*. McGraw-Hill, New York, pp 393–399
  49. Rossi S, Balestreri M, Spagnoli D, Bellinzona G, Valeriani V, Bruzzone P, Maestri M, Stocchetti N (2000) Oxygen delivery and oxygen tension in cerebral tissue during global cerebral ischemia: a swine model. *Acta Neurochir (Wien) [Suppl]* 76: 199–202
  50. Rossi S, Stocchetti N (1999) Comment: brain tissue oxygenation. *J Neurosurg* 91: 1065–1067
  51. Sahuquillo J, Amoros S, Santos A, Poca MA, Panzardo H, Dpmique L, Pedraza S (2000) Does an increase in cerebral perfusion pressure always mean better oxygenated brain? A study in head-injured patients. *Acta Neurochir (Wien) [Suppl]* 76: 457–462
  52. Sarrafzadeh A, Kiening K, Bardt T, Schneider G, Unterberg A, Lanksch W (1998) Cerebral oxygenation in contused vs nonlesioned brain tissue: monitoring of PtiO<sub>2</sub> with Licox and Paratrend. *Acta Neurochir (Wien) [Suppl]* 71: 186–189
  53. Sarrafzadeh A, Sakowitz OW, Callsen TA, Lanksch WR, Unterberg AW (2002) Detection of secondary insults by brain tissue pO<sub>2</sub> and bedside microdialysis in severe head injury. *Acta Neurochir (Wien) [Suppl]* 81: 319–321
  54. Schneider GH, Sarrafzadeh A, Kiening KL, Bardt TF, Unterberg AW, Lanksch WR (1998) Influence of hyperventilation on brain tissue-PO<sub>2</sub>, PCO<sub>2</sub> and pH in patients with intracranial hypertension. *Acta Neurochir (Wien) [Suppl]* 71: 62–65
  55. Schousboe A, Westergaard N, Waagepetersen H, Larsson O, Bakken I, Sonnewald U (1997) Trafficking between glia and neurons of TCA cycle intermediates and related metabolites. *Glia* 21: 99–105
  56. Schurr A, Miller J, Payne R, Rigor B (1999) An increase in lactate output by brain tissue serves to meet the energy needs of glutamate-activated neurons. *J Neurosci* 19: 34–39
  57. Schurr A, West C, Rigor B (1988) Lactate supported synaptic function in the rat hippocampal slice preparation. *Science* 240: 1326–1328
  58. Siesjö B (1978) *Brain energy metabolism*. Wiley, Chichester New York Brisbane Toronto
  59. Singer MM, Wright F, Stanley LK, Roe BB, Hamilton WK (2002) Oxygen toxicity in man: a prospective study in patients after open-heart surgery. *N Engl J Med* 283: 1473–1478
  60. Stahl N, Ungerstedt U, Nordstrom C (2001) Brain energy metabolism during controlled reduction of cerebral perfusion pressure in severe head injuries. *Intensive Care Med* 27: 1215–1223
  61. Steiner LA, Czosnyka M, Piechnik S, Smielewski P, Chatfield D, Menon DK, Pickard JD (2002) Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Crit Care Med* 30: 733–738
  62. Stocchetti N, Chiaregato A, De Marchi M, Croce M, Benti R, Grimoldi N (1998) High cerebral perfusion pressure improves low values of local brain tissue O<sub>2</sub> tension (PtiO<sub>2</sub>) in focal lesions. *Acta Neurochir (Wien) [Suppl]* 71: 162–165
  63. Thomas S, Prins M, Samii M, Hovda D (2000) Cerebral metabolic response to traumatic brain injury sustained early in development: a 2-deoxy-D-glucose autoradiographic study. *J Neurotrauma* 17: 649–665
  64. Van de Water JM, Kagey KS, Miller IT (2002) Response of the lung to six to 12 hours of 100% oxygen inhalation in normal man. *N Engl J Med* 283: 621–626
  65. van den Brink W, van Santbrink H, Steyerberg E, Avezaat CJ, Suazo JA, Hogesteegeer C, Jansen WJ, Kloos LM, Vermeulen J, Maas A (2000) Brain oxygen tension in severe head injury. *Neurosurgery* 46: 868–876
  66. VanSantbrink H, Maas A, Avezaat C (1996) Continuous monitoring of partial pressure of brain tissue oxygen in patients with severe head injury. *Neurosurgery* 38: 21–31
  67. Yoshino A, Hovda D, Kawamata T (1991) Dynamic changes in local cerebral glucose utilization following cerebral concussion in rats: evidence of a hyper and a subsequent hypometabolic state. *Brain Res* 561: 106–119
  68. Young B, Runge JW, Waxman KS (1996) Effects of pegorgotein on neurologic outcome of patients with severe head injury. *JAMA* 276: 538–543
  69. Zauner A, Bullock R, Young HF (1995) Continuous monitoring of brain oxygen, CO<sub>2</sub>, pH and temperature in brain tissue using a single sensor. *J Neurotrauma* 12: 468
  70. Zauner A, Clausen T, Alves OL, Rice A, Levasseur J, Young HF, Bullock R (2002) Cerebral metabolism after fluid-percussion injury and hypoxia in a feline model. *J Neurosurg* 97: 643–649

## Comment

This prospective observation cohort study, conducted on 20 patients with severe head injury describes the effects of increasing FiO<sub>2</sub> on brain tissue PtiO<sub>2</sub>, lactate and glucose concentrations in microdialysate of the brain and further describes the relation between CPP and brain tissue PtiO<sub>2</sub>. Monitoring of brain tissue oxygen tension and microdialysis were introduced into clinical practice approximately 10 years ago. Microdialysis has remained mainly confined to research settings, but the technique of brain tissue oxygen monitoring has, partly because of its simplicity, gained wide acceptance in neuro intensive care and is now routinely employed in many centers. Studies in TBI have shown a frequent occurrence of low values of PtiO<sub>2</sub> in the initial 12 to 24 hours and the occurrence of such values is related to poorer outcome. We are now at the turning point where results of this currently accepted monitoring technique can be translated into improved therapeutic strategies, aiming at increasing the chances for better outcome in individual patients. This manuscript represents a significant step forward in this direction. The authors convincingly demonstrate that increasing FiO<sub>2</sub> improves brain tissue oxygen tension. They further show that during the oxygen challenge period of 6 hours lactate levels are lower in microdialysate of the brain than in the following period. These observations would support the concept for improving cerebral oxygenation following severe head injury by simply increasing FiO<sub>2</sub>. There remain however many clinical and also basic questions which need to be answered before this approach should be routinely adopted in neuro-intensive care. Somewhat unfortunately this manuscript focuses on means and averages in the population described. This approach for goes opportunities for individualized targeted management based on multimodality monitoring. It may well be that for instance the slope of diffusion of oxygen between the arterial circulation and the brain tissue may be relevant. The authors for instance described that in patients in whom low PtiO<sub>2</sub> was not increased on elevating FiO<sub>2</sub> fatal outcome occurred in 4 out of 6 cases; presumably in the other 2 cases in which this phenomenon was observed, the local values were influenced by the presence of hemorrhage contusions. This observation highlights the limitations and potential pitfalls of a regional technique. It should further be recognized that measured values of PtiO<sub>2</sub> with the technique employed represent average values from the recruitment area surrounding the probe. This recruitment area is determined by the number, spatial distribution and diameter of local vessels contributing to tissue perfusion. In this regard equal

attention should be paid to improving local microcirculation as well as it to improving  $\text{FiO}_2$ . The observation from the Lorentzian analysis showing a peak of  $\text{PtiO}_2$  at a CPP of 78 mmHg is of interest and would support the concept of maintaining CPP between 70 and 80 mmHg. However here again the limitations of analysis of averages is pertinent and hopefully in the future more targeted values in individual patients can be determined by results of multimodality monitoring.

Although the authors correctly state that prospective randomised clinical studies will be required to demonstrate clinical efficacy of oxygen targeted management in head injury I doubt whether such will be achievable and is in fact even necessary. Personally I would

be quite happy if functional studies such as fMRI or PET studies would show positive effects of oxygen targeted management on cerebral function.

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